Amendments to the Specification

Please replace the indicated paragraphs below:

Page1- Page 2:

[0004] Paliperidone is more fully described in US Pat. No. ~~4,804,663~~ 5,158,952. The paliperidone compound differs from risperidone and related prior art compounds described in US Pat. Nos. 4,804,663, 4,352,811 and 4,458,076 by its 9-OH substitution ~~on the 1-position of the piperdine moiety~~.

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[0018] Devices in which a drug composition is delivered in a dry state from a large exit orifice by the action of an expandable layer are described in US Patent Nos. 4,892,778, 4,915,949 and 4,940,465. Those references describe a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall 20 containing a layer of expandable material that pushes a dry drug layer out of the compartment formed by the wall 20. The exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall 20.

[0022] US Patent Nos. 4,892,778 and 4,940,465, describe a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall 20 containing a layer of expandable material that pushes a drug layer out of the compartment formed by the wall 20. The exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall 20.

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[0023] US Patent No. 4,915,949, describes a dispenser for delivering a beneficial agent to an environment of use that includes a semipermeable wall 20 containing a layer of expandable

material that pushes a drug layer out of the compartment formed by the wall 20. The drug layer contains discrete tiny pills dispersed in a carrier. The exit orifice in the device is substantially the same diameter as the inner diameter of the compartment formed by the wall 20.

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[00068] The expressions "exit," "exit orifice," "delivery orifice" or "drug delivery orifice," and other similar expressions, as may be used herein include a member selected from the group consisting of a passageway; an aperture; an orifice; and a bore. The expression also includes an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall 20 to thereby form an exit orifice. The expression includes one or multiple passageways, apertures, orifices, bores or pores.

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[00086] Osmotic dosage forms, in general, utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semipermeable wall 20 that permits free diffusion of fluid but not drug or osmotic agent(s), if present. A significant advantage to osmotic systems is that operation is pH-independent and thus continues at the osmotically determined rate throughout an extended time period even as the dosage form transits the gastrointestinal tract and encounters differing microenvironments having significantly different pH values. A review of such dosage forms is found in Santus and Baker, "Osmotic drug delivery: a review of the patent literature," Journal of Controlled Release 35 (1995) 1-21. In particular, the following U.S. Patents, owned by the assignee of the present application, ALZA Corporation, directed to osmotic dosage forms, are each incorporated in their entirety herein: Nos. 3,845,770; 3,916,899; 3,995,631; 4,008,719;

4,111,202; 4,160,020; 4,327,725; 4,519,801; 4,578,075; 4,681,583; 5,019,397; and 5,156,850.

Page 23 – Please delete paragraph **[000107]**

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[000113] Additional semipermeable polymers for forming wall 20 comprise cellulose acetaldehyde dimethyl acetate; cellulose acetate ethylcarbamate; cellulose acetate methyl carbamate; cellulose dimethylaminoacetate; semipermeable polyamide; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; cross-linked selectively semipermeable polymers formed by the coprecipitation of an anion and a cation, as disclosed in U.S. Patents Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142; semipermeable polymers, as disclosed by Loeb, et al. in U.S. Patent No. 3,133,132; semipermeable polystyrene derivatives; semipermeable poly(sodium styrenesulfonate); semipermeable poly(vinylbenzyltrimethylammonium chloride); and semipermeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-2} (cc. mil/cm hr.atm), expressed as per atmosphere of hydrostatic or osmotic pressure differences across a semipermeable wall 20. The polymers are known to the art in U.S. Patents Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott and Roff (1971) CRC Press, Cleveland, OH.

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[000114] Wall 20 may also comprise a flux-regulating agent. The flux regulating agent is a compound added to assist in regulating the fluid permeability or flux through wall 20. The flux-regulating agent can be a flux-enhancing agent or a flux-decreasing agent. The agent can be preselected to increase or decrease the liquid flux. Agents that produce a marked increase in permeability to fluid such as water are often essentially hydrophilic, while those that produce a marked decrease to fluids such as water are essentially hydrophobic. The

amount of regulator in the wall 20 when incorporated therein generally is from about 0.01% to 20% by weight or more. The flux regulator agents may include polyhydric alcohols, polyalkylene glycols, polyalkylenediols, polyesters of alkylene glycols, and the like. Typical flux enhancers include polyethylene glycol 300, 400, 600, 1500, 4000, 6000 and the like; low molecular weight glycols such as polypropylene glycol, polybutylene glycol and polyamylene glycol: the polyalkylenediols such as poly(1,3-propanediol), poly(1,4-butanediol), poly(1,6-hexanediol), and the like; aliphatic diols such as 1,3-butylene glycol, 1,4-pentamethylene glycol, 1,4-hexamethylene glycol, and the like; alkylene triols such as glycerine, 1,2,3-butanetriol, 1,2,4-hexanetriol, 1,3,6-hexanetriol and the like; esters such as ethylene glycol dipropionate, ethylene glycol butyrate, butylene glycol dipropionate, glycerol acetate esters, and the like. Presently preferred flux enhancers include the group of difunctional block-copolymer polyoxyalkylene derivatives of propylene glycol known as pluronics (BASF). Representative flux-decreasing agents include phthalates substituted with an alkyl or alkoxy or with both an alkyl and alkoxy group such as diethyl phthalate, dimethoxyethyl phthalate, dimethyl phthalate, and [di(2-ethylhexyl) phthalate], aryl phthalates such as triphenyl phthalate, and butyl benzyl phthalate; insoluble salts such as calcium sulfate, barium sulfate, calcium phosphate, and the like; insoluble oxides such as titanium oxide; polymers in powder, granule and like form such as polystyrene, polymethylmethacrylate, polycarbonate, and polysulfone; esters such as citric acid esters esterified with long chain alkyl groups; inert and substantially water impermeable fillers; resins compatible with cellulose based wall 20 forming materials, and the like.

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[000115] Other materials may be included in the semipermeable wall 20 composition for imparting flexibility and elongation properties, for making wall 20 less brittle and to render tear strength. Suitable materials include phthalate plasticizers such as dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, straight chain phthalates of six to eleven carbons, di-isononyl phthalte, di-isodecyl phthalate, and the like. The plasticizers include nonphthalates such as triacetin, dioctyl azelate, epoxidized tallate, tri-isoctyl trimellitate, tri-isononyl trimellitate, sucrose acetate isobutyrate, epoxidized soybean oil, and the like. The amount of plasticizer in a wall 20 when incorporated therein is about 0.01% to 20% weight, or higher.

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[000121] Figure 3 illustrates the preferred embodiment of dosage form 10 including the protective inner wall 20 or subcoat 90 and an optional third component barrier layer 55 separating second component drug layer 40 from push layer 50.

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[000128] Inner wall 90 also reduces friction between the external surface of drug layer 30 and drug layer 40, and the inner surface of wall 20. Inner wall 90 promotes release of the drug composition from the compartment and reduces the amount of residual drug composition remaining in the compartment at the end of the delivery period, particularly when the slurry, suspension or solution of the drug composition that is being dispensed is highly viscous during the period of time in which it is being dispensed. In dosage forms in which there is high drug loading, i.e., 40% or greater active agent in the drug layer based on the overall weight of the drug layer, and no inner wall 20, it has been observed that significant residual amounts of drug may remain in the device after the period of delivery has

been completed. In some instances, amounts of 20% or greater may remain in the dosage form at the end of a twenty-four hour period when tested in a release rate assay.

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[000131] Inner wall 90 typically may be 0.01 to 5 mm thick, more typically 0.5 to 5mm thick, and it comprises a member selected from hydrogels, gelatin, low molecular weight polyethylene oxides, e.g., less than 100,000 MW, hydroxyalkylcelluloses, e.g., hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcelluose, hydroxybutylcellulose and hydroxyphenylcellulose, and hydroxyalkyl alkylcelluloses, e.g., hydroxypropyl methylcellulose, and mixtures thereof. The hydroxyalkylcelluloses comprise polymers having a 9,500 to 1,250,000 number-average molecular weight. For example, hydroxypropyl celluloses having number average molecular weights of between 80,000 to 850,000 are useful. The inner wall 20 may be prepared from conventional solutions or suspensions of the aforementioned materials in aqueous solvents or inert organic solvents.

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[000132] Preferred materials for the inner wall 20 include hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, povidone [poly(vinylpyrrolidone)], polyethylene glycol, and mixtures thereof.

[000133] Most preferred are mixtures of hydroxypropyl cellulose and povidone, prepared in organic solvents, particularly organic polar solvents such as lower alkanols having 1-8 carbon atoms, preferably ethanol, mixtures of hydroxyethyl cellolose and hydroxypropyl methyl cellulose prepared in aqueous solution, and mixtures of hydroxyethyl cellulose and polyethylene glycol prepared in aqueous solution. Most preferably, the inner wall 20 comprises a mixture of hydroxypropyl cellulose and providone prepared in ethanol.

[000135] Conveniently, the weight of the inner wall 20 applied to the compressed core may be correlated with the thickness of the inner wall 20 and residual drug remaining in a dosage form in a release rate assay such as described herein. As such, during manufacturing operations, the thickness of the inner wall 20 may be controlled by controlling the weight of the inner wall 20 taken up in the coating operation.

[000136] When inner wall 90 is formed as a subcoat, i.e., by coating onto the tabletted composite including one or all of the first drug layer, second drug layer and push layer, the inner wall 20 can fill in surface irregularities formed on the core by the tabletting process. The resulting smooth external surface facilitates slippage between the coated composite core and the semipermeable wall 20 during dispensing of the drug, resulting in a lower amount of residual drug composition remaining in the device at the end of the dosing period. When inner wall 90 is fabricated of a gel-forming material, contact with water in the environment of use facilitates formation of the gel or gel-like inner coat having a viscosity that may promote and enhance slippage between outer wall 20 and drug layer 30 and drug layer 40.

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[000139] Pan coating may be conveniently used to provide the completed dosage form, except for the exit orifice. In the pan coating system, the wall 20 forming composition for the inner wall 20 or the outer wall 20, as the case may be, is deposited by successive spraying of the appropriate wall 20 composition onto the compressed trilayered or multilayered core comprising the drug layers, optional barrier layer and push layer, accompanied by tumbling in a rotating pan. A pan coater is used because of its availability at commercial scale. Other techniques can be used for coating the compressed core. Once coated, the wall 20 is dried in a forced-air oven or in a temperature and humidity controlled oven to free the dosage form of

solvent(s) used in the manufacturing. Drying conditions will be conventionally chosen on the basis of available equipment, ambient conditions, solvents, coatings, coating thickness, and the like.

[000140] Other coating techniques can also be employed. For example, the wall 20 or walls 20 of the dosage form may be formed in one technique using the air-suspension procedure. This procedure consists of suspending and tumbling the compressed core in a current of air and the semipermeable wall 20 forming composition, until the wall 20 is applied to the core. The air-suspension procedure is well suited for independently forming the wall 20 of the dosage form. The air-suspension procedure is described in U.S. Patent No. 2,799,241; in J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and, ibid., Vol. 49, pp. 82-84 (1960). The dosage form also can be coated with a Wurster® air-suspension coater using, for example, methylene dichloride methanol as a cosolvent for the wall 20 forming material. An Aeromatic® air-suspension coater can be used employing a cosolvent.

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[000141] Dosage forms in accord with the present invention are manufactured by standard techniques. For example, the dosage form may be manufactured by the wet granulation technique. In the wet granulation technique, the drug and carrier are blended using an organic solvent, such as denatured anhydrous ethanol, as the granulation fluid. The remaining ingredients can be dissolved in a portion of the granulation fluid, such as the solvent described above, and this latter prepared wet blend is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass blend is then forced through a predetermined screen onto oven trays. The blend is dried for 18 to 24 hours at 24□C to 35□C in a forced-air oven. The dried

granules are then sized. Next, magnesium stearate, or another suitable lubricant, is added to the drug granulation, and the granulation is put into milling jars and mixed on a jar mill for 10 minutes. The composition is pressed into a layer, for example, in a Manesty® press or a Korsch LCT press. For a trilayered core, granules or powders of the drug layer compositions and push layer composition are sequentially placed in an appropriately-sized die with intermediate compression steps being applied to each of the first two layers, followed by a final compression step after the last layer is added to the die to form the trilayered core. The intermediate compression typically takes place under a force of about 50-100 newtons. Final stage compression typically takes place at a force of 3500 newtons or greater, often 3500-5000 newtons. The compressed cores are fed to a dry coater press, e.g., Kilian® Dry Coater press, and subsequently coated with the wall 20 materials as described above.

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[000143] In another manufacture the drug and other ingredients comprising the drug layer are blended and pressed into a solid layer. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form, and it also possesses dimensions corresponding to the push layer, if included, for forming a contacting arrangement therewith. The drug and other ingredients can also be blended with a solvent and mixed into a solid or semisolid form by conventional methods, such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. Next, if included, a layer of osmopolymer composition is placed in contact with the layer of drug in a like manner. The layering of the drug formulation and the osmopolymer layer can be fabricated by conventional two-layer press techniques. An analogous procedure may be followed for the preparation of the trilayered core. The compressed cores then may be coated

with the inner wall 20 material and the semipermeable wall 20 material as described above.

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[000146] Exit 60 may include an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall 20 to thereby form an exit orifice. The substance or polymer may include, for example, an erodible poly(glycolic) acid or poly(lactic) acid in the semipermeable wall 20; a gelatinous filament; a water-removable poly(vinyl alcohol); a leachable compound, such as a fluid removable pore-former selected from the group consisting of inorganic and organic salt, oxide and carbohydrate.

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[000150] Drilling, including mechanical and laser drilling, through the semipermeable wall 20 can be used to form the exit orifice. Such exits and equipment for forming such exits are disclosed in U.S. Patents Nos. 3,916,899, by Theeuwes and Higuchi and in U.S. Patent No. 4,088,864, by Theeuwes, et al. It is presently preferred to utilize two exits of equal diameter.

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[000154] A dosage form adapted, designed and shaped as an osmotic drug delivery device is manufactured as follows: A first drug compartment is prepared as follows: 100 g of paliperidone, 7345 g of polyethylene oxide with average molecular weight of 200,000, and 200 g of sodium chloride, USP are added to a fluid bed granulator bowl. Next a binder solution is prepared by dissolving 800 g of hydroxypropylmethyl cellulose identified as 2910 having an average viscosity of 5 cps in 9,200 g of water. The dry materials are fluid bed granulated by spraying with 6750 g of binder solution. Next, the wet granulation is dried in the granulator to an acceptable moisture content, and sized using by passing through a 7-

mesh screen. Next, the granulation is transferred to a blender and mixed with 5 g of butylated hydroxytoluene as an antioxidant and lubricated with 50 g of stearic acid.

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[000158] The trilayered arrangements are coated with a subcoat laminate. The wall 20 forming composition comprises 70% hydroxypropyl cellulose identified as EF, having an average molecular weight of 80,000 and 30% of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000. The wall-forming composition is dissolved in anhydrous ethyl alcohol, to make an 8% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 20 mg of laminate is applied to each tablet.

[000159] The trilayered arrangements are coated with a semi-permeable wall 20. The wall forming composition comprises 99% cellulose acetate having a 39.8% acetyl content and 1% polyethylene glycol comprising a 3.350 viscosity-average molecular weight. The wall-forming composition is dissolved in an acetone:water (95:5 wt:wt) co solvent to make a 5% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 45 mg of membrane is applied to each tablet.

[000160] Next, two 25 mil (0.6 mm) exit passageways are laser drilled through the semi-permeable wall 20 to connect the drug layer with the exterior of the dosage system. The residual solvent is removed by drying for 144 hours as 45 C. and 45% humidity. After drilling, the osmotic systems are dried for 4 hours at 45 C. to remove excess moisture.

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[000161] The dosage form produced by this manufacture is designed to deliver 1.9 mg of paliperidone in an ascending delivery pattern from two drug-containing cores. First core contains 1% paliperidone, 73.45% polyethylene oxide possessing a 200,000 molecular weight, 20% sodium chloride, USP, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. Second drug core contains 2.8% paliperidone, 91.65% polyethylene oxide possessing a 200,000 molecular weight, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. The push composition is comprised 73.7% polyethylene oxide comprising a 7,000,000 molecular weight, 20% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 1% ferric oxide, 0.05% butylated hydroxytoluene, and 0.25% magnesium stearate. The semi permeable wall 20 is comprised of 99% cellulose acetate of 39.8% acetyl content and 1% polyethylene glycol. The dosage form comprises two passageways, 25 mils (0.6 mm) on the center of the drug side.

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[000167] The trilayered arrangements are coated with a semi-permeable wall 20. The wall forming composition comprises 99% cellulose acetate having a 39.8% acetyl content and 1% polyethylene glycol comprising a 3.350 viscosity-average molecular weight. The wall-forming composition is dissolved in an acetone:water (95:5 wt:wt) co solvent to make a 5% solids solution. The wall-forming composition is sprayed onto and around the bilayered arrangements in a pan coater until approximately 39 mg of membrane is applied to each tablet.

[000168] Next, two 25 mil (0.6 mm) exit passageways are laser drilled through the semi-permeable wall 20 to connect the drug layer with the exterior of the dosage system. The residual solvent is removed by drying for 144 hours as 45 C. and 45% humidity. After drilling, the osmotic systems are dried for 4 hours at 45 C to remove excess moisture.

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[000169] The dosage form produced by this manufacture is designed to deliver 0.25 mg of paliperidone in an ascending delivery pattern from two drug-containing cores. First core contains 0.25% paliperidone, 74.20% polyethylene oxide possessing a 200,000 molecular weight, 20% sodium chloride, USP, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. Second drug core contains 0.7% paliperidone, 93.75% polyethylene oxide possessing a 200,000 molecular weight, 5% hydroxypropylmethyl cellulose having an average viscosity of 5 cps, 0.05% butylated hydroxytoluene, and 0.5% stearic acid. The push composition is comprised 73.7% polyethylene oxide comprising a 7,000,000 molecular weight, 20% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 1% ferric oxide, 0.05% butylated hydroxytoluene, and 0.25% magnesium stearate. The semi permeable wall 20 is comprised of 99% cellulose acetate of 39.8% acetyl content and 1% polyethylene glycol. The dosage form comprises two passageways, 25 mils (0.6 mm) on the center of the drug side.

Amendments to the Figures

Please replace Fig. 1 with the attached substituted Fig. 1 showing changes in red ink.